Comment re: "Sporadic Aberrant Crypt Foci Are Not a Surrogate Endpoint for Colorectal Adenoma Prevention" and "Aberrant Crypt Foci in the Adenoma Prevention with Celecoxib Trial"

In Response: We have several comments in response to the robust rebuttal by Stevens et al. of the conclusions in our Perspective (1) on the report "Aberrant Crypt Foci (ACF) in the Adenoma Prevention with Celecoxib Trial" by Cho et al. (2). In that Perspective, we reviewed at some length the numerous studies conducted in ACF tissue that mechanistically assessed the molecular pathogenesis of colorectal neoplasia; we did not and do not dispute that many of the molecular features of colorectal tumorigenesis can be identified in selected human ACF tissues.

Stevens et al. affirm that "there is a long and impressive history of preclinical animal studies showing that ACF suppression is associated with reduced cancer incidence," and we began our article by describing this body of work. However, they do not challenge our conclusion that "the relevance of preclinical ACF research to the clinical setting is undefined." We point out that proponents of ACF as valuable biomarkers for evaluating human colorectal neoplasia have failed to provide good evidence that carcinogen-induced ACF in rodents and morphologically similar human ACF can be equated for functional and pathophysiologic significance.

We agree with Stevens et al. that major methodologic issues about the clinical ascertainment of human ACF at chromoendoscopy remain unresolved. We also note that they do not refute our point that the technical challenges of applying this technology, such as the lack of magnifying endoscopes in most clinical endoscopy facilities and the inability of most endoscopists to spend the additional time required for rigorous ACF assessment, have seriously restricted its application. The fact that it was feasible to undertake the ACF substudy at only 5 of the 91 clinical sites where the parent Adenoma Prevention with Celecoxib trial was conducted is eloquent testimony to the restricted applicability of ACF technology.

As we pointed out in our Perspective, carcinogen-induced rodent ACF were first reported more than 20 years ago in 1987 (3). Human ACF were first reported in 1991 by Pretlow et al. (4), one of the letter authors to whom we respond here. Results of the study by Takayama et al. (5), which probably did more than any other single study to raise expectations for the study of human ACF, were published 10 years ago. Given the report of Cho et al. (2) and over two decades of evaluation without any good evidence of validation, we stand fully behind the conclusion in our Perspective that ACF cannot be justified as a surrogate end point in colorectal cancer chemoprevention trials. We respectfully point out that we arrived at this conclusion not "based on…[our] 'diverse perspectives'" of expertise, as stated by Stevens and colleagues, but "*from* our diverse perspectives" and based on our objective interpretation of the ACF data in the literature. The call for more research is a familiar cry. In this case, the onus is firmly on the advocates to provide the long-elusive evidence that ACF are a useful end point in colorectal cancer prevention studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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